

We claim:

1. A DNA construct encoding a chimeric protein comprising
 - (a) at least one receptor domain capable of binding to a selected ligand, and
 - (b) a heterologous protein domain capable of initiating apoptosis in a cell containing said chimeric protein following exposure of the cell to the ligand,
said ligand being capable of binding to two or more chimeric protein molecules.
2. A DNA construct of claim 1 wherein the chimeric protein further comprises an intracellular targeting domain capable of directing the chimeric protein to a desired cellular compartment.
3. A DNA construct of claim 2 wherein the intracellular targeting domain comprises a secretory leader sequence, a membrane spanning domain, a membrane binding domain or a sequence directing the protein to associate with vesicles or with the nucleus.
4. A DNA construct of claim 1 wherein the chimeric protein has a K_d value for binding to the selected ligand of less than or equal to about 10^{-6} M.
5. A DNA construct of claim 1 wherein the selected ligand is less than about 5 kDa in molecular weight.
6. A DNA construct of claim 1 wherein the heterologous protein domain comprises the cytoplasmic domain of human Fas or a human TNF α receptor.
7. A DNA construct of claim 1 wherein the chimeric protein is capable of binding to an FK506-type ligand, a cyclosporin A-type ligand, tetracycline or a steroid ligand.
8. A DNA vector containing a DNA construct of claim 1 and a selectable marker permitting transfection of the DNA construct into host cells and selection of transfectants containing the construct.

9. A DNA vector of claim 8 wherein the vector is a viral vector.

10. A viral vector of claim 9 which is an adeno-, adeno associated- or retroviral vector.

11. A chimeric protein encoded by a DNA construct of claim 1.

12. A cell containing and capable of expressing at least one DNA construct of claim 1.

13. A cell of claim 12 characterized by the ability to become apoptotic and die following contact with the selected ligand.

14. A cell of claim 12 which is a mammalian cell.

15. A cell of claim 13 which further contains

(a) a DNA construct encoding a chimeric protein comprising (i) at least one receptor domain capable of binding to a second selected ligand and (ii) another protein domain, heterologous with respect to the receptor domain, but capable, upon oligomerization with one or more other like domains, of triggering the activation of transcription of a target gene under the transcriptional control of a transcriptional control element responsive to said oligomerization; and

(b) a target gene under the expression control of a transcriptional control element responsive to said oligomerization;

and which is capable of expressing the target gene following exposure of the cell to said second selected ligand.

16 A cell of claim 13 which contains a series of DNA constructs encoding

(a) a first additional chimeric protein containing a DNA-binding domain and at least one receptor domain capable of binding to a first selected ligand moiety ; and

TOGETHER WITH A REPORT

(b) a second additional chimeric protein containing a transcriptional activating domain and at least one receptor domain capable of binding to a second selected ligand (which may be the same or different from the first selected ligand moiety); and

and a second DNA construct encoding a target gene under the transcriptional control of a heterologous transcriptional control sequence which binds with the DNA-binding domain and is responsive to the transcriptional activating domain;

which cell expresses the target gene following exposure to a substance containing the selected ligand moiety(ies).

17. The use, to prepare a pharmaceutical composition for ablating a population of genetically engineered cells of claim 13, of a ligand capable of initiating apoptosis with said cells, said ligand having the formula:



wherein n is an integer from 2 to about 5, rbm(1)-rbm(n) are receptor binding moieties which may be the same or different and which are capable of binding to the chimeric protein(s), said rbm moieties being covalently attached to a linker moiety which is a bi- or multi-functional molecule capable of being covalently linked ("—") to two or more rbm moieties.

18. The use, of claim 17, of a ligand to prepare a pharmaceutical composition for ablating a population of genetically engineered cells wherein the ligand has a molecular weight less than about 5 kDa.

19. The use, of claim 17, of a ligand to prepare a pharmaceutical composition for ablating a population of genetically engineered cells wherein the ligand comprise an FK506-type moiety, a cyclosporin-type moiety, a steroid or tetracycline

20. The use, of claim 17, of a ligand to prepare a pharmaceutical composition for ablating a population of genetically engineered cells wherein the

ligand binds to a naturally occurring receptor with a K_d value greater than about 10^{-5} M.

21. The use, of claim 17, of a ligand to prepare a pharmaceutical composition for ablating a population of genetically engineered cells wherein the ligand comprises a molecule of FK506, FK520, rapamycin or a derivative thereof modified at C9, C10 or both.
22. The use, of claim 20, of a ligand to prepare a pharmaceutical composition for ablating a population of genetically engineered cells wherein the ligand contains a linker moiety comprising a C2-C20 alkylene, C4-C18 azalkylene, C6-C24 N-alkylene azalkylene, C6-C18 arylene, C8-C24 ardialkylene or C8-C36 bis-carboxamido alkylene moiety.
23. A method for ablating a population of genetically engineered cells of claim 13 which comprises exposing the cells to a ligand, capable of binding to the chimeric protein, in an amount effective to result in initiating cell death.
24. A method of claim 23 wherein the cells are grown in a culture medium and the exposing is effected by adding the ligand to the culture medium.
25. A method of claim 23 wherein the cells are present within a host organism and the exposing is effected by administering the ligand to the host organism.
26. A method of claim 25 wherein the host organism is a mammal and the ligand is administered by oral, bucal, sublingual, transdermal, subcutaneous, intramuscular, intravenous, intra-joint or inhalation administration in an appropriate vehicle therfor.
27. A method for producing a cell which may be selectively killed which comprises introducing a DNA construct of claim 1 into a host cell.
28. A method of claim 27 which further comprises selecting those cells containing the introduced DNA construct.
29. A kit which comprises at least one DNA construct of claim 1.

30. A kit of claim 29 which further comprises a ligand to which one or more of the chimeric proteins encoded by the DNA construct(s) bind.
31. A kit of claim 29 which further comprises a monomeric ligand reagent as an antagonist for ligand-chimeric protein binding.
32. A host organism containing a cell of any of claim 12.
33. A host organism of claim 32 which is a plant or animal organism.
34. An animal of claim 33 which is a worm, insect or mammal.
35. A mammal of claim 34 which is a mouse or other rodent or a human.

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